JC07 Rec'd PCT/PTO 22 OCT 2001

FORM PTO-1390 (REV. 9-2001) U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: 97473 US

U S APPLICATION NO (If known, see 37 CFR 1 5): TO BE ASSIGNED 10/031797

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP00/03747	25-APR-2000	29-APR-1999

TITLE OF INVENTION: USE OF ANTIPROGESTAGENS IN COMBINED THERAPY

APPLICANT(S) FOR DO/EO/US: COELINGH BENNINK, Herman J.T. ET AL.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [ ] This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. [X] The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is attached hereto (required only if not communicated by the International Bureau).
   b. [X] has been communicated by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [ ] An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. [ ] is attached hereto.
   b. [ ] has been previously submitted under 35 U.S.C. 154(d)(4).
7. [X] Amendments to the claims of the International Aplication under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are attached hereto (required only if not communicated by the International Bureau).
   b. [ ] have been communicated by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [X] have not been made and will not be made.
8. [ ] An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. [ ] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] An English lanugage translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. [X] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [X] A FIRST preliminary amendment.
14. [ ] A SECOND or SUBSEQUENT preliminary amendment.
15. [ ] A substitute specification.
16. [ ] A change of power of attorney and/or address letter.
17. [ ] A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
18. [ ] A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. [ ] A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. [ ] Other items or information:

EXPRESS MAIL NO. EL 839703452 US

531 Rec'd PCT/PTO 22 OCT 2001

U.S. APPLICATION NO. (If known, see 37 CFR 1.5) 10/088737 TO BE ASSIGNED	INTERNATIONAL APPLICATION NO PCT/EP00/03747	ATTORNEY'S DOCKET NUMBER 97473 US

21. [X] The following fees are submitted:	CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1040.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$890.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$740.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$710.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$890.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	16- 20 =		x **$18.00**	$	
Independent claims	6 - 3 =	3	x **$84.00**	$252.00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ **$280.00**	$	
TOTAL OF ABOVE CALCULATIONS =				$252.00	
[ ] Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2. +				$	
SUBTOTAL =				$1,142.00	
Processing fee of **$130.00** for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				$	
TOTAL NATIONAL FEE =				$	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$	
TOTAL FEES ENCLOSED =				$	
				Amount to be refunded:	$
				charged:	$ 1,142.00

a. [ ] A check in the amount of $ _____ to cover the above fees is enclosed.

b. [X] Please charge my Deposit Account No. 02-2334 in the amount of $ 1,142. to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 02-2334 A duplicate copy of this sheet is enclosed.

d. [ ] Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:
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SIGNATURE

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NAME

29,772
REGISTRATION NUMBER

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

COELINGH BENNINK, Herman J.T.; DECKERS, Godefridus H.J.; DOLS, Paul P.M.A.; ORLEMANS, Everardus O.M.; SCHOONEN, Wilhelmus G.E.J.

Serial No.: To be assigned Group Art Unit: To be assigned

Filed: October 29, 2001 Examiner: To be assigned

For: USE OF ANTIPROGESTAGENS IN COMBINED THERAPY

Corresponding to: PCT/EP00/03747, filed April 25, 2000

PRELIMINARY AMENDMENT

Assistant Commissioner of Patents
Washington, D.C. 20231

October 22, 2001

Sir:

Prior to examining the present application, please enter the amendments that follow:

IN THE CLAIMS:

Please replace claims 2 and 4-9 with amended claims 2 and 4-9.

Please cancel claims 1 and 3 without prejudice or disclaimer of the subject matter thereof, and add new claims 10-18.

2. (Amended) The method according to claim 11, wherein the intermittent administration of Org 33245 takes place as an addition to progestagen-only therapy.

4. (Amended) The method of claim 11, wherein Org 33245 is administered for 1-7 days during a cycle of 28-32 days, wherein one dosage marks the end of a cycle and the optional other dosages are administered regularly divided over the remaining days of the cycle.

5. (Amended) A contraceptive kit for the daily administration of a progestagen and for the intermittent administration of an anti-progestagen, comprising a progestagen dosage unit and an anti-progestagen dosage unit, wherein the anti-progestagen dosage unit comprises Org 33245.

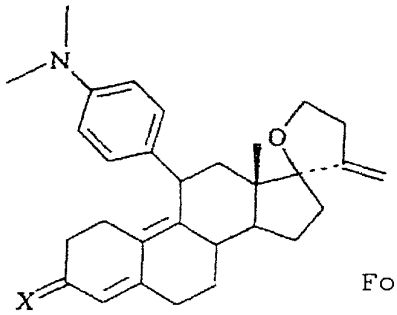
6. (Amended) A combined dosage unit comprising a progestagen and an anti-progestagen, wherein the anti-progestagen is Org 33245.

7. (Amended) A method of contraception comprising daily administering to a female of childbearing age a contraceptively effective amount of a progestagen and intermittently administering an anti-progestagen, wherein the anti-progestagen is Org 33245.

8. (Amended) A method of treatment of irregular or breakthrough uterine bleeding in a female using a progestagen-only preparation, comprising intermittently administering an anti-progestagen, wherein the anti-progestagen is Org 33245.

9. (Amended) The method according to claim 7, wherein the anti-progestagen is administered on 1-4 days in a cycle of 28-32 days.

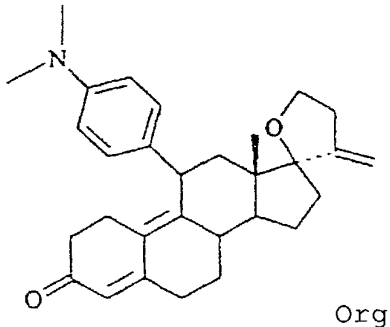
-- 10. A method of anti-progestagen therapy, comprising administering an effective amount of the anti-progestagen of Formula II



Formula II

wherein X is selected from the group consisting of (H,H), (O) and (N-OH), or a salt thereof, said anti-progestagen being administered intermittently, whereby the time between each pair of sequentially administered doses of anti-progestagen is greater than one day. --

-- 11. A method of anti-progestagen therapy, comprising administering an effective amount of the anti-progestagen Org 33245



Org 33245

or a salt thereof, said anti-progestagen being administered intermittently, whereby the time between each pair of sequentially administered doses of anti-progestagen is greater than one day. --

-- 12. The method of claim 11, wherein the anti-progestagen therapy is hormone replacement therapy. --

-- 13. The method claim 11, wherein the anti-progestagen therapy is contraception. --

-- 14. The method of claim 11, wherein the anti-progestagen therapy is for minimizing uterine bleeding. --

-- 15. The method according to claim 8, wherein the anti-progestagen is administered on 1-4 days in a cycle of 28-32 days. --

-- 16. The method of claim 10, wherein the anti-progestagen therapy is hormone replacement therapy. --

-- 17. The method of claim 10, wherein the anti-progestagen therapy is contraception. --

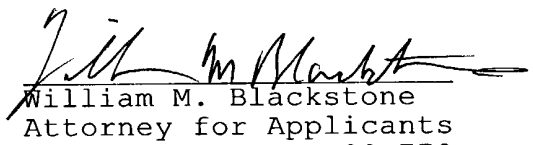
-- 18. The method of claim 10, wherein the anti-progestagen therapy is for minimizing uterine bleeding. --

REMARKS

Claims 2 and 4-9 are amended and claims 1 and 3 are cancelled. Claims 2, 4-9 and 10-18 are presented for examination. These amendments are made prior to examination without limiting the scope of the claims as first written. These amendments are not made for reasons of patentability under 35 U.S.C. 101, 102, 103 or 112 and no estoppel is created hereby.

It is believed that claims 2, 4-9 and 10-18 recite a patentable improvement in the art. Favorable action is solicited. In the event any fees are required with this paper, please charge our Deposit Account No. 02-2334.

Respectfully submitted,



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WMB:lcf
101COELINGH-BENNINK-PREAMENDMENT

VERSION WITH MARKINGS TO SHOW CHANGES MADE

2. (Amended) [A use] The method according to [claim 1, characterised in that] claim 11, wherein the intermittent administration of Org 33245 takes place as an addition to progestagen-only therapy.

4. (Amended) [A use according to any of the preceding claims, characterised in that a dosage of] The method of claim 11, wherein Org 33245 is [to be] administered for 1-7 days during a cycle of 28-32 days, wherein one dosage marks the end of a cycle and the optional other dosages [to be] are administered regularly divided over the remaining days of the cycle.

5. (Amended) A contraceptive kit [providing means (a)] for the daily administration of a progestagen and [means (b)] for the intermittent administration of an anti-progestagen, [wherein the latter means (b) comprises as the anti-progestagen the compound] comprising a progestagen dosage unit and an anti-progestagen dosage unit, wherein the anti-progestagen dosage unit comprises Org 33245 [as defined in the description].

6. (Amended) A combined [means for the] dosage unit [of] comprising a progestagen and an anti-progestagen, [characterised in that] wherein the anti-progestagen is Org 33245 [as defined in the description].

7. (Amended) A method of contraception comprising daily administering to a female of childbearing age a contraceptively effective amount of a progestagen and intermittently administering an anti-progestagen, wherein the anti-progestagen is Org 33245 [as defined in the description].

8. (Amended) A method of treatment of irregular or breakthrough uterine bleeding in a female using a progestagen-only preparation, comprising intermittently administering an

anti-progestagen, wherein the anti-progestagen is Org 33245 [as defined in the description].

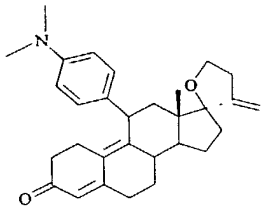
9. (Amended) [A] The method according to claim 7 [or 8], wherein the anti-progestagen is administered on 1-4 days in a cycle of 28-32 days.

USE OF ANTIPROGESTAGENS IN COMBINED THERAPY

The invention pertains to an anti-progestagenic steroid of the 11β-aryl, 17-spiromethylene type. Such antiprogestational compounds are known from EP 549041 and EP 582338. As described, their therapeutic use is associated with several advantages, int.al. in view of a strong activity and high selectivity, in which these compounds are markedly distinct from RU 486, which holds as the reference anti-progestagen in the field.

The invention is particularly concerned with a field of use of anti-progestagens wherein the anti-progestagen is not a daily therapy, but is used intermittently, i.e. not daily or continuously, but in a regimen of administration wherein each administration of anti-progestagen is followed by one or more days without anti-progestagen. More particularly, such an intermittent use will be in conjunction with other medication, such as progestagen-only therapy.

It has now been found that, within the above known group of 11β-aryl, 17-spiromethylene steroids, one compound has a surprisingly better suitability than the others for being administered intermittently. This is the compound satisfying the structural formula I given below, hereinafter referred to as Org 33245:



Formula I

This particular compound therewith has the highly advantageous property that it can be used in the specific medical application of combined therapy with progestagen-only preparations.

Progestagen-only preparations for contraception or HRT (hormone replacement therapy) are known. Contraceptive regimens of this type are usually referred to as "progestagen-only pill' or "POP". Such POPs have the general advantage of avoiding the administration of estrogens. It is known to use anti-progestagens in order to improve the effects of the administration of progestagen-only preparations. This particularly relates to an improved bleeding pattern. Thus major improvements have been proposed, according to which the anti-progestagen is administered periodically, which leads to bleeding patterns that more closely resemble the natural menstrual cycle. One such improvement is that according to Hodgen, see WO 93/21927, wherein a contraceptive regimen free from estrogens is described, in which the active, ovulation-inhibiting ingredient is a progestational agent, and wherein an anti-progestagen is administered intermittently in order to achieve better bleeding (int.al. minimizing progestagen-associated breakthrough bleeding). The anti-progestagen is administered e.g. once every 30, 60, 90, or 120 days, and preferably once every cycle of 30 days (most preferably on day 28 of each cycle). Another such improvement is that according to WO 97/49407, in which it is described to administer, in addition to a progestagen-only preparation, two to seven dosage units comprising an anti-progestagen, one of which is administered at the beginning of a cycle, the other or others divided regularly throughout the cycle (which is described as being 20-32 days and preferably 28).

The concept of a "progestagen only" therapy as indicated above should not be confused with therapies or contraceptive methods in which both the progestagen and the anti-progestagen are administered for a number of consecutive days, as one multi-day phase in a multiphase regimen. Such a regimen is known from, e.g., WO 94/04156 wherein a contraceptive kit is disclosed which provides a first phase of 5-20 sequential daily dosage units containing an anti-progestagen and a second phase of 10-25 sequential daily dosage units containing a progestagen.

It has been found that, surprisingly, Org 33245 not only has a strong activity and high selectivity, but also shows a strong binding to human orosomucoid, which is indicative of a relatively long half life (Steingold et al. 1990, American Journal of Obstetrics and Gynaecology 162, 532-524). This makes the compound extremely well suitable for intermittent administration, and much better so than anti-progestagens proposed earlier for this use, such as RU 486 and Org 33628.

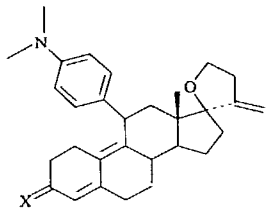
It should be noted that the excellent suitability of Org 33245 comes all the more as a surprise since this could not be expected from the closely related progestagen Org 33628 which, in fact, has been proposed for use in the regimens described in EP 549041 and EP 582338. Org 33628, although being highly advantageous from the perspective of cost-price and activity, suffers from a drawback particularly associated with intermittent use. This drawback is its relatively rapid metabolism, as can be seen from the short half-life in humans (about 12 hours). This confronts the person skilled in the art with the problem of finding an alternative which has the advantages of Org 33628, but does not have this drawback.

The invention obviates this drawback and provides the use of Org 33245 in the manufacture of a contraceptive or HRT agent wherein Org 33245 is to be administered intermittently, the intermission between each pair of sequentially administered dosage units of anti-progestagen being more than 1 day. The invention particularly is in the use of Org 33245 for the manufacture of a preparation for the intermittent administration thereof in the course of progestagen-only therapy (including contraception). Put otherwise, the invention includes a method of treatment involving progestagen-only therapy in combination with the intermittent administration of Org 33245. The invention also pertains to a combination comprising a progestagen and an anti-progestagen, wherein the anti-progestagen is Org 33245.

The term "intermittent" should not be confused with the term "non-continuous." A regular, sequential daily administration (in which one administration, e.g. a daily

tablet, is naturally followed by e.g. 24 hours of pause until the next daily administration occurs) is not an intermittent administration as defined in the context of the present invention. As used herein, the term "intermittent" should be understood as being related to a "sequential daily administration" in such way that it could be referred to as a "sequential non-daily intermittent administration." I.e., when in a given sequence of days a sequential daily administration means one dosage unit every day of the sequence (e.g. a tablet), then sequential non-daily administration means that each administration is followed by a pause-period comprising at least one day on which no anti-progestagen is administered, and said pause period is followed by another administration of anti-progestagen. In other words, intermittent administration according to the invention requires that the intermission between each pair of sequentially administered anti-progestagen units is more than 1 day. Clearly, with the intermission being 2 days or longer, the problem incurred with Org 33628 and solved with Org 33245 is all the more eminent.

As will be easily understood by the person skilled in the art, it is intended to include in the invention the compound of formula I, as well as prodrugs and precursors thereof, i.e. those closely related compounds the substituents of which are easily metabolised to the active compound according to formula I, or are readily cleaved to such a compound upon being administered. Together with the most regular prodrugs, the invention thus pertains to the compounds satisfying formula II, and pharmaceutically acceptable salts thereof.



Formula II

wherein X stands for (H,H), (O), or (N-OH); The 3-keto compound, i.e. Org 33245 itself in which X is (O), is preferred. The other possibilities for the substituent at carbon atom number 3 have as their main property according to the invention that they

are precursors (prodrugs) of the preferred 3-keto compound. For the sake of clarity, the invention is described hereinafter with reference to Org 33245 itself.

For the preparation of Org 33245 reference is made to EP 549041 and EP 582338, more specifically Example 1 of EP 549041. In the intermittent use according to the invention, Org 33245 will generally be employed in a dosage amount ranging from 0.1 to 300 mg, and preferably 0.5 to 150 mg. The dosage amount of Org 33245 can be the same each time it is administered, but it may also be used in decreasing amounts as described in WO 97/49407.

The type of administration of Org 33245 can be any type of dsaoge unit which is suitable for intermittent administration, i.e. it could include an injection which can be given once or several times a month, or it could include a transdermal patch which is applied and removed again once or several times a month, in each case leaving the majority of days without the administration of Org 33245. However, the most convenient and desired form for the intermittent administration of Org 33245 is by way of an oral dosage unit, preferably a tablet.

The intermittent administration of Org 33245 is particularly advantageous in the course of progestagen-only therapy (including contraception). While the anti-progestagen is given intermittently, i.e. on certain days only, it is preferred that on such a day, it is administered together with the progestagen dosage. While an anti-progestagen with a too rapid metabolism will require a precise point in time of administration, and not necessarily simultaneously with the progestagen, Org 33245 can be given in a form physically combined with the progestagen. Thus the invention also includes a combined dosage unit comprising a progestagen and an anti-progestagen, wherein the anti-progestagen is Org 33245.

The invention includes a drug delivery system for contraceptive use (a contraceptive kit) containing daily oral dosage units, each unit containing a progestagen, and 1-7,

preferably 1-4 units comprising an anti-progestagen, preferably combined with the progestagen. One of the anti-progestagen dosage units is administered at the end (or, for that matter, the beginning) of a cycle. In fact the anti-progestagen dosage which is given once a cycle, marks the transition from one cycle to the next (i.e. the term "end of the cycle" can be interpreted as the "beginning" of a cycle as well). A second anti-progestagen dosage unit, if given, is administered in the middle of the cycle. If more than two anti-progestagen dosage units are employed, one is given at the end of a cycle, the others orderly divided through the cycle. The preferred dosage regimens are those specifically described in WO 93/21927 and WO 97/49407. The term "cycle" refers to a period of generally 20-35 days, and preferably more close to the natural menstrual cycle, i.e. 28-32 days.

The invention also includes a drug delivery system for HRT (hormone replacement therapy) containing daily oral dosage units, each unit comprising a progestagen with or without an estrogen or an estrogen only, and 1-7, preferably 1-4 dosage units comprising an anti-progestagen, one of which is preferably administered at the beginning of a cycle and the others orderly divided through the cycle (if one other: in the middle of the cycle).

In general terms the invention relates to a contraceptive and/or HRT (hormone replacement therapy) kit comprising sequential daily dosage units for oral administration each comprising as the sole contraceptively effective ingredient a progestagen, or as effective ingredient for HRT a progestagen with or without an estrogen or an estrogen alone, and further two or more units comprising an anti-progestagen.

If desired the kits may contain placebo pills to bridge two periods of administration of active ingredients.

The invention also includes a pharmaceutical product (i.e. the dosage units or the package containing the dosage units), a method of using the product, and a process of manufacturing the pharmaceutical product.

The invention also includes a method of providing contraception and/or HRT for a pre-, peri-, or post-menopausal woman involving administering to the woman the above-mentioned regimens. Thus, the invention also resides in a method of contraception comprising daily administering to a female of child-bearing age a contraceptively effective amount of a progestagen and intermittently administering an anti-progestagen, wherein the anti-progestagen is Org 33245. In another aspect, the invention resides in a method of treatment of irregular or breakthrough bleeding in a female using a progestagen-only preparation, comprising intermittenty administering Org 33245. In these methods it is preferred if Org 33245 is administered on 1-4 days in a cycle of 28-32 days, divided over said cycle, with one of the administrations usually considered the end (or, for that matter, the beginning) of a cycle.

Progestagens for use with the invention are 3-keto-desogestrel (etonogestrel), desogestrel, gestodene, levonorgestel, norgestrel and other progestagens commonly used for contraception and HRT. Desogestrel has the chemical name 13-ethyl-11-methylene-18,19-di-nor-17α-pregn-4-en-20-yn-17-ol, and is the preferred progestagen. Desogestrel is believed to be metabolized in the body into 3-ketodesogestrel. Preferably, the dosage units contain 75 μg of desogestrel or 3-ketodesogestrel, or an amount of other progestagens having the equivalent effect of 75 μg of desogestrel. Based on practically applied doses, levonorgestrel, desogestrel, and 3-keto-desogestrel are relatively equipotent in progestagenic activity. Gestodene is approximately 1.5 times as potent as these compounds. Norgestrel is about half as potent as levonorgestrel. A further preferred progestagen is Org 30659, see int. al. EP 897927.

The invention will be explained further with reference to the following examples.

Example 1

Org 33245 ((11ß,17α)-17,23-epoxy-11-[(4-dimethylamino)phenyl]-19,24-dinorchola-4,9,20-trien-3-one) is synthesized according to Example 1 of EP 549041.

Example 2

A range of pharmaceutical compositions is prepared containing a steroid in accordance with the present invention. Org 33245 is mixed with the other ingredients in a standard way, and the mixture is subjected to granulation.

The composition is as follows:

Org 33245 (active)	1-10 wt.%;
Corn Starch (disintegrant)	15 wt.%;
Hydroxy Propyl Cellulose (binder)	3 wt.%;
Lactose 200 M (diluent) up to	100 wt.%;

The resulting granules can be used for tabletting following procedures regularly available in the art, so as to make a dosage unit suitable for use in the invention.

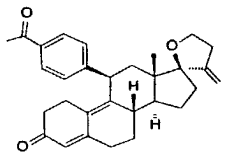
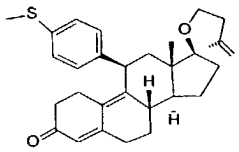
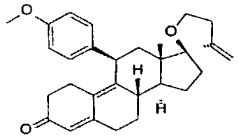
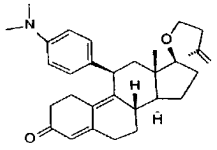
Example 3

Of several anti-progestagens the binding to orosomucoid is determined as described in Philibert et al., Antihormones in Health and Disease (M.K. Agarwal, ed.), 1991, 19, 1-17. The results are depicted in the Table below. The results show that, while the binding of the other anti-progestagens tested is lower than that of RU 486 (100%), Org 33245 constitutes a marked improvement.

Example 4

Anti-progestagenic activity is determined by using an anti-McPhail test as known to the person skilled in the art and described, int.al., in Kloosterboer et al., Human Reproduction (1994), Volume 9, Supplement 1, pages 47-52. Results in terms of the Minimum Active Dose (MAD) are given in the Table below.

TABLE

Compound	Binding affinity to orosomucoid (relative to RU 486)	Anti-McPhail Assay (MAD)
	13,5 %	8 mg/kg
	82 %	> 1 mg/kg
	64 %	1 mg/kg
	222 %	0.5 mg/kg

Claims:

1. The use of Org 33245 as defined in the description for the manufacture of a contraceptive or HRT agent wherein Org 33245 is to be administered intermittently, the intermission between each pair of sequentially administered dosage units of anti-progestagen being more than one day.

2. A use according to claim 1, characterised in that the intermittent administration of Org 33245 takes place as an addition to progestagen-only therapy.

3. The use of Org 33245 for the manufacture of a medicament for minimizing uterine bleeding in a female using a progestin-only pharmaceutical preparation, characterized in that the anti-progestagen is Org 33245 as defined in the description.

4. A use according to any of the preceding claims, characterised in that a dosage of Org 33245 is to be administered 1-7 days during a cycle of 28-32 days, wherein one dosage marks the end of a cycle and the optional other dosages are to be administered regularly divided over the remaining days of the cycle.

5. A contraceptive kit providing means (a) for the daily administration of a progestagen and means (b) for the intermittent administration of an anti-progestagen, wherein the latter means (b) comprises as the anti-progestagen the compound Org 33245 as defined in the description.

6. A combined means for the dosage of a progestagen and an anti-progestagen, characterised in that the anti-progestagen is Org 33245 as defined in the description.

7. A method of contraception comprising daily administering to a female of child-bearing age a contraceptively effective amount of a progestagen and intermittently administering an anti-progestagen, wherein the anti-progestagen is Org 33245 as defined in the description.

8. A method of treatment of irregular or breakthrough uterine bleeding in a female using a progestagen-only preparation, comprising intermittenty administering an anti-progestagen, wherein the anti-progestagen is Org 33245 as defined in the description.

9. A method according to claim 7 or 8, wherein the anti-progestagen is administered on 1-4 days in a cycle of 28-32 days.

PCT

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International Bureau

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99201390.4 29 April 1999 (29.04.99) EP

(71) Applicant *(for all designated States except US)*: AKZO NOBEL N.V. [NL/NL]; Velperweg 76, NL–6824 AB Arnhem (NL).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: COELINGH BENNINK, Herman, Jan, Tijmen [NL/NL]; Melvill van Carnbeelaan 38, NL–3971 BE Driebergen (NL). DECKERS, Godefridus, Hermanus, Johanna [NL/NL]; van Limburg Stirumstraat 34, NL–5344 HW Oss (NL). DOLS, Paul, Peter, Marie, Antonius [NL/NL]; Ringelenburg 1, NL–5346 VR Oss (NL). ORLEMANS, Everardus, Otto, Maria [NL/NL]; Wolvespoor 12, NL–5343 XM Oss (NL). SCHOONEN, Wilhelmus, Gerardus, Eduardus, Joseph [NL/NL]; Parklaan 16, NL–5345 BV Oss (NL).

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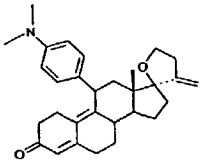
(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: USE OF ANTIPROGESTAGENS IN COMBINED THERAPY



(I)

(57) Abstract

It has been found that the compound satisfying structural formula (I) has a surprisingly good suitability for being administered intermittently. This particular compound therewith has the highly advantageous property that is can be used in the specific medical application of combined therapy with progestagen–only preparations.

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION

#4

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

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USA

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Full name of sole or first inventor **Coelingh Bennink, Herman, Jan, Tijmen**
Inventor' signature _____
Citizenship the Netherlands **DUTCH** Date May 13 2002

Residence and P.O.Address **Melvill v Carnbeelaan 38**
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The Netherlands

Full name of sole or first inventor **Deckers, Godefridus, Hermanus, Johanna**
Inventor's signature _____
Date

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Residence and P.O.Address **c/o: N.V. Organon**
Patent Department
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5340 BH Oss
The Netherlands

Full name of third joint inventor **Dols, Paul, Peter, Marie, Antonius**

Inventor's signature _____
Date

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Residence and P.O.Address **c/o: N.V. Organon**
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The Netherlands

(5).
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Full name of forth joint inventor **Orlemans, Everardus, Otto, Maria**

Inventor's signature _____

Date

Citizenship **DUTCH**

Residence and P.O.Address **c/o: N.V. Organon**
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5340 BH Oss
The Netherlands

Full name of fifth joint inventor **Schoonen, Wilhelmus, Gerardus, Eduardus, Joseph**

Inventor's signature _____

Date

Citizenship **DUTCH**

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Patent Department
Postbus 20
5340 BH Oss
The Netherlands

Full name of sixth joint inventor _____

Inventor's signature _____

Date

Citizenship _____

Residence and P.O.Address _____

Full name of seventh joint inventor _____

Inventor's signature _____

Date

Citizenship _____

Residence and P.O.Address _____

Full name of eighth joint inventor _____

Inventor's signature _____

Date

Citizenship _____

Residence and P.O.Address _____

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Inventor' signature _____

Citizenship **DUTCH** Date _____

Residence and P.O.Address **Melvill v Carnbeelaan 38**
3971 BE Driebergen
The Netherlands

2 - co
Full name of sole or ~~first~~ inventor **Deckers, Godefridus, Hermanus, Johanna**
Inventor's signature _____ 10 - May - 2002
Date

Citizenship **DUTCH**
Residence and P.O.Address **c/o: N.V. Organon**
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The Netherlands

Full name of third joint inventor **Dols, Paul, Peter, Marie, Antonius**

Inventor's signature _____
Date

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Residence and P.O.Address **c/o: N.V. Organon**
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5340 BH Oss
The Netherlands

Over to 3rd elec

Full name of forth joint inventor **Oriemans, Everardus, Otto, Maria**

Inventor's signature _____

Date

Citizenship **DUTCH**

Residence and P.O.Address **c/o: N.V. Organon**
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The Netherlands

Full name of fifth joint inventor **Schoonen, Wilhelmus, Gerardus, Eduardus, Joseph**

Inventor's signature _____

Date

Citizenship **DUTCH**

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Patent Department
Postbus 20
5340 BH Oss
The Netherlands

Full name of sixth joint inventor _____

Inventor's signature _____

Date

Citizenship _____

Residence and P.O.Address _____

Full name of seventh joint inventor _____

Inventor's signature _____

Date

Citizenship _____

Residence and P.O.Address _____

Full name of eighth joint inventor _____

Inventor's signature _____

Date

Citizenship _____

Residence and P.O.Address _____

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Inventor' signature _____

Citizenship **DUTCH** Date _____

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3971 BE Driebergen
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Inventor's signature _____
Date

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3-00
Full name of third joint inventor **Dols, Paul, Peter, Marie, Antonius**

Inventor's signature _____ May 10th 2002
Date

Citizenship **DUTCH**
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Inventor's signature _____

Date

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Residence and P.O.Address **c/o: N.V. Organon**
Patent Department
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The Netherlands

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Inventor's signature _____

Date

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Inventor's signature _____

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Inventor's signature _____

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Full name of third joint inventor **Dols, Paul, Peter, Marie, Antonius**

Inventor's signature _____
Date

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4 - 00

Full name of forth joint inventor **Orlemans, Everardus, Otto, Maria**

Inventor's signature _____ May 15, '02
Date

Citizenship **DUTCH**

Residence and P.O.Address **c/o: N.V. Organon**
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Postbus 20
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Full name of fifth joint inventor **Schoonen, Wilhelmus, Gerardus, Eduardus, Joseph**

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5340 BH Oss
The Netherlands

Full name of sixth joint inventor _____

Inventor's signature _____
Date

Citizenship _____

Residence and P.O.Address _____

Full name of seventh joint inventor _____

Inventor's signature _____
Date

Citizenship _____

Residence and P.O.Address _____

Full name of eighth joint inventor _____

Inventor's signature _____
Date

Citizenship _____

Residence and P.O.Address _____

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Number	Country	Day/Month/Year filed	

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application(s) in the manner provided by the

first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose to the patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56(a) which became available between the filing date of the prior application(s) and the national or PCT international filing date of this application.

(U.S. Serial No.) (Filing date) (Status-patented, pending, abandoned)

(U.S. Serial No. (Filing date) (Status-patented, pending, abandoned)

And I hereby appoint as principal attorney, William M. Blackstone, Registration No. 29,772 and Michael G. Sullivan, Registration No. 35,377.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued theron.

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Full name of sixth joint inventor _____

Inventor's signature _____

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Full name of seventh joint inventor _____

Inventor's signature _____

Date

Citizenship _____

Residence and P.O.Address _____

Full name of eighth joint inventor _____

Inventor's signature _____

Date

Citizenship _____

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